Hot off the Press

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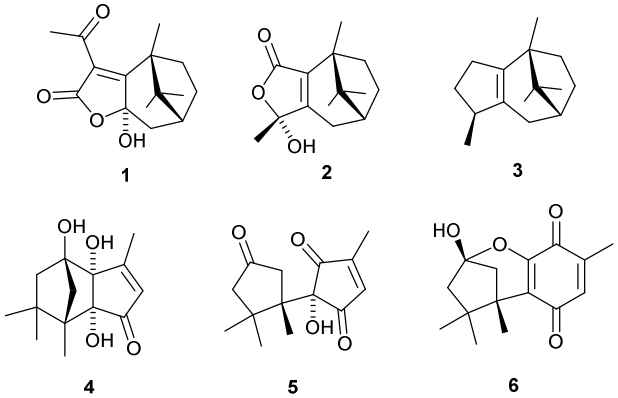
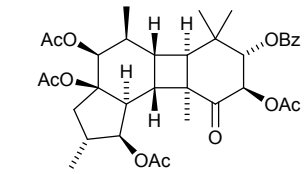
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as caesalpinflavin A from *Caesalpina enneaphylla*.

Pocahemiketals A **1** and B **2**, isolated from *Pogostemon cablin*, have new sesquiterpenoid skeletons that are proposed to be formed from β-patchoulene **3**.[1] The norsesquiterpenoid metabolites hitoyols A **4** and B **5**, isolated from the basidiomycete *Coprinopsis cinerea*, also have new skeletons.[2] Biosynthetic pathways to hitoyols A **4** and B **5** from the cuparane co-metabolite lagopodin B **6** have been proposed. The structures of pocahemiketal B **2** and hitoyol A **4** were confirmed by X-ray amalysis.



The new skeleton of gaditanone **7**, a constituent of *Euphorbia gaditana*, is proposed to be formed by [2+2] cycloaddition of a jatrophane diterpenoid precursor.[3] This hypothesis was confirmed by UV irradiation of the jatrophane **8** to produce gaditanone **7** in 97% yield. The structure of aphapolin A **9**, from *Aphanamixis*

polystachya, was confirmed by X-ray analysis.[4] A [2+2] cycloaddition of the co-constituent diterpenoid **10** is thought to be involved in a formation of aphapolin A **9**. The racemic sesterterpenoid metabolite hippolide J **11**, from the marine sponge *Hippospongia lachne*, is also thought to be formed by a [2+2] cycloaddition.[5]



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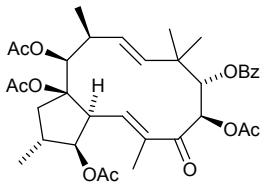

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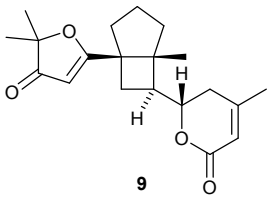

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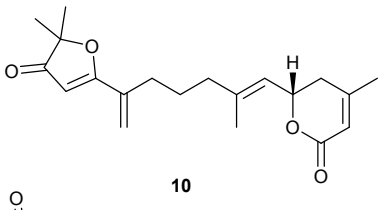

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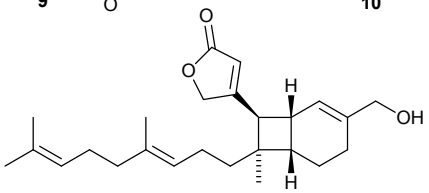

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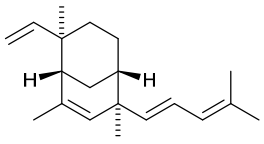
The new skeleton of the diterpenoid xishacorene A **12**, from *Sinularia polydactyla*, is proposed to be formed biosynthetically from the co-metabolite fuscol **13**.[6] Phylanes A **14** and B **15**, from the roots of *Phyllanthus acidus*, also have new diterpenoid skeltons that probably arise from a cleistanthane precursor.[7] Further new diterpenoid skeletons are found in euphodraculoates A **16** and B **17** from *Euphorbia dracunuloides*.[8] Biosynthetic pathways from a tigliane precursor to euphodraculoates A **16** and B **17** have been proposed.



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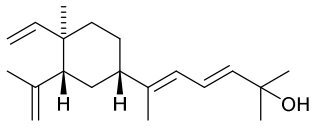

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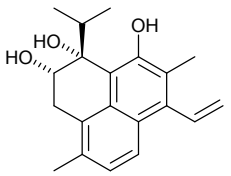

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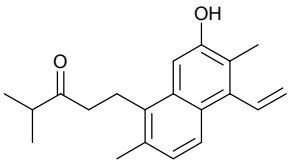

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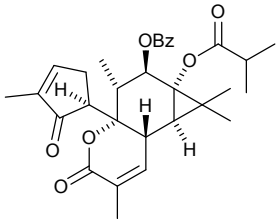

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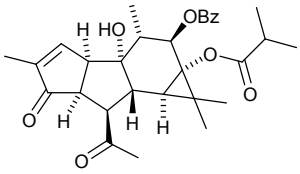
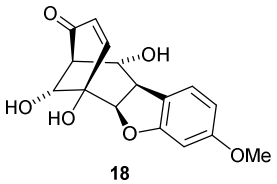


17

Sophopterocarpan A **18**, from the roots of *Sophora flavescens*, has a novel skeleton that is proposed to be formed biosynthetically from medicarpin **19**.[9] An unusual bridged system is present in the hybrid flavan-chalcone caesalpinflavan A **20** isolated from *Caesalpina enneaphylla*.[10] The structures of sophopterocarpan A **18** and caesalpinflavan A **20** were established by X-ray analyses. Deletion of the COP9 signalosome subunit *PfcsnE* from *Pestalotiopsis fici* produced five new metabolites including pestaloficin A **21** that is a new type of dimeric cyclohexane derivative linked through a spirocyclopentene ring.[11]



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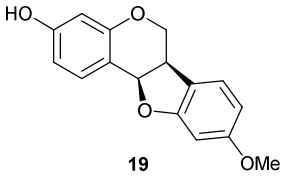

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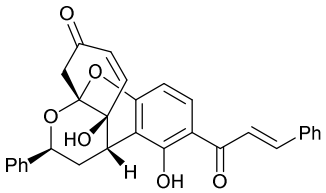

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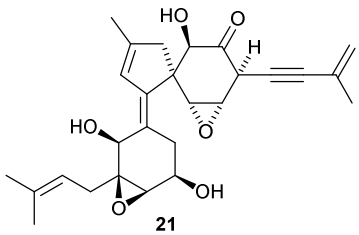
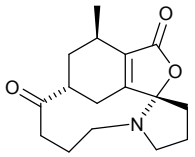


21

The structure of lycoplanine A **22**, from the club moss *Lycopodium complanatum*, was established by X-ray analysis.[12] The normonoterpenoid indole alkaloid rauvomine B **23**, from *Rauvolfia vomitoria*, has an unusual 6/5/6/6/3/5 hexacyclic ring system.[13] Biosynthetic pathways to produce the novel skeletons of lycoplanine A **22**

and rauvomine B **23** have been proposed. Tetra(indol-3-yl)ethanone **24**, a metabolite of marine-derived *Pseudovibrio denitrificans*, showed interesting cytotoxic properties.[14]



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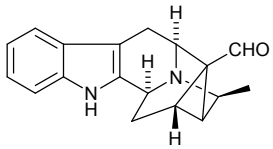

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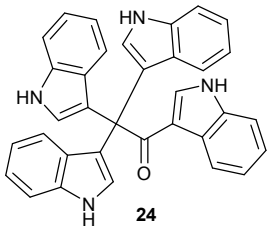

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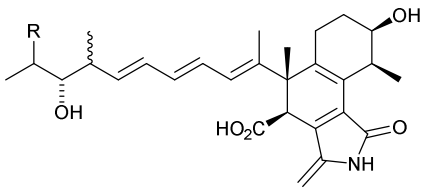
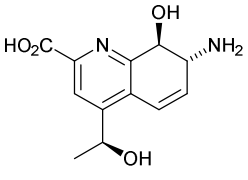
Pyxipyrrolones A **25** and B **26**, from a strain of the genus *Pyxidicoccus*, are representatives of a new class of myxobacterial metabolites.[15] Pyxipyrrolone B **26** shows interesting cytotoxic properties. Genome sequencing of the producer strain has enabled a biosynthetic pathway to pyxipyrrolones A **25** and B **26** to be proposed. Quinaldic acid **27** is an important subunit in the antibiotic thiostrepton. Biosynthetic studies have established that the quinoline ring system is formed by ring expansion of 2-methyltryptophan by a newly found strategy.[16]



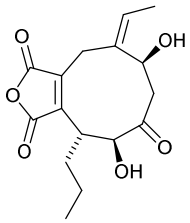
25 R = CH_3
26 R = H



27

The biosynthetic pathway of the herbicide cornexistin **28** in the fungus *Paceilomyces variotii* has been characterised using a combination of genome sequencing, gene knockout and isolation of the resulting intermediates.[17] The early stages of the cornexistin pathway resembles other nonadrides but requires fewer enzymes for later steps such as nonadride dimerisation. The biosynthetic pathway of azaphilone

pigments such as rubropunctatin **29** has been elucidated in *Monascus ruber* M7.[18] Using targeted gene knockouts and heterologous gene expression has shown the origin of yellow pigments from a shunt pathway and their conversion to orange pigments through an enzyme catalysed transformation.



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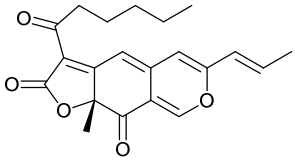

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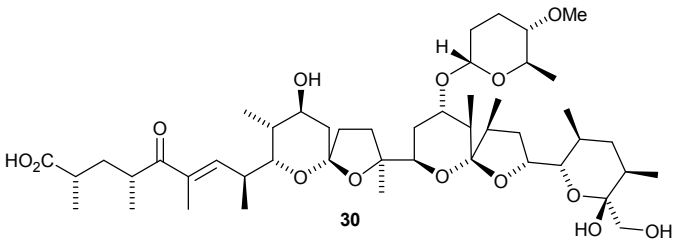
A new tandem modules epimerase assay has been used to investigate the dehydratase (DH) domains in polyketide synthase (PKS) modules that produce epimerised (2*S*)-2-methyl-3-keto-acyl-ACP.[19] The assay revealed the epimerase and dehydratase activity of a range of epimerase-active DH domains such as that found of the nanchangmycin **30** PKS. The use of fungal artificial chromosomes (FAC) and metabolomic scoring (MS) has provided a scalable process for the characterisation of secondary metabolites and their gene clusters in filamentous fungi.[20] Application of the FAC-MS platform for the screening of 56 secondary metabolite biosynthetic gene clusters for expression in *Aspergillus nidulans* led to the discovery of 15 new metabolites such as the macrolactone, valactamide A **31**.



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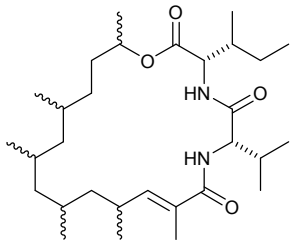
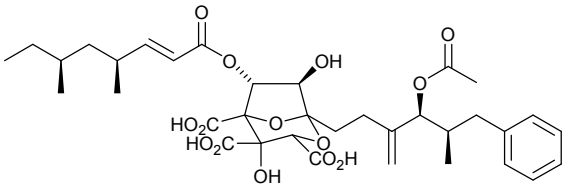


31

The enzymes of the initial steps of the biosynthetic pathway of the potent cholesterol-lowering agent, zaragozic acid **32** have been studied by reconstitution in the heterologous host, *Aspergillus nidulans*.[21] These studies identified the three enzymes that are required for the biosynthesis of the benzoyl portion of the natural product and a tricarboxylic acid product that may act as the starting point for generation of the dioxobicyclic core. The entire biosynthetic pathway of cyclindrocyclophane F **33** has been elucidated, revealing an enzyme that performs a biosynthetic version of a Friedel-Crafts alkylation.[22] A novel metal-dependent halogenase enzyme was shown to chlorinate an unactivated carbon centre and this was followed by a dimerisation reaction involving sequential stereospecific alkylation of resorcinol aromatic rings by the newly characterised alkylating enzyme.



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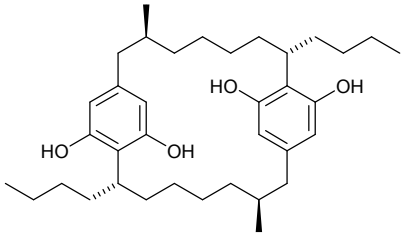

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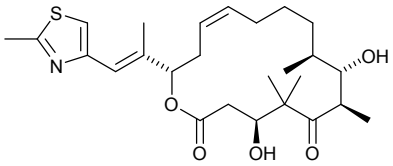
Heterologous production of the potent anticancer drugs epothilones (e.g. epothilone C **34**) has been significantly improved using a novel electroporation procedure.[23] Introduction of the epothilone biosynthetic gene cluster from the myxobacterium *Sorangium cellulosum* using the electroporation procedure into the chromosome of *Burkholderiales* strain DSM 7029 resulted in a 75-fold increase in the total yields of the epothilones. Isolation and characterisation of a heme-dependent enzyme, KtzT from the *Kutzneria* species 744 has identified its role in the formation of N-N bonds

of piperazates, found in a wide range of natural products such as kutzneride 2 **35**.[24] The authors suggest that this work will expedite the isolation of new piperazate-containing natural products via targeted genome mining.



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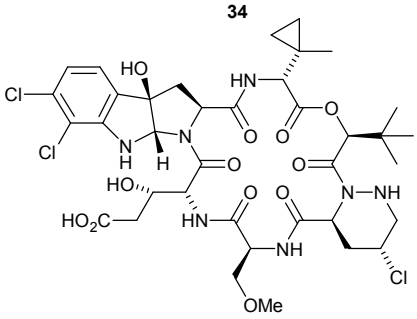
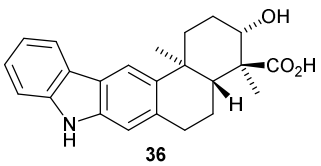


35

A flavoenzyme, XiaK from the biosynthetic pathway of the indolosesquiterpene xiamycin A **36** has been characterised as an *N*-hydroxylase and shown to catalyse the in vivo production of a range of products through C-Cl, C-N and N-N bond formation.[25] In vitro, XiaK was shown to catalyse only hydroxylation of xiamycin A at the carbazole nitrogen, forming a compound that is proposed to lead to the multiple xiamycin A adducts via radical pathways. Characterisation of the AmbU isomerocyclases in the ambiguine pathway has revealed the biosynthetic origin of hapalindole U **37**.[26] A calcium-dependent AmbU1-U4 enzymatic complex was shown to catalyse the cascade formation of hapalindole U via various transformations, including a Cope rearrangement and a stereodivergent aza-Prins cyclisation.



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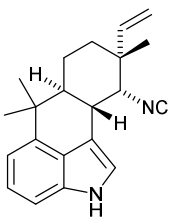

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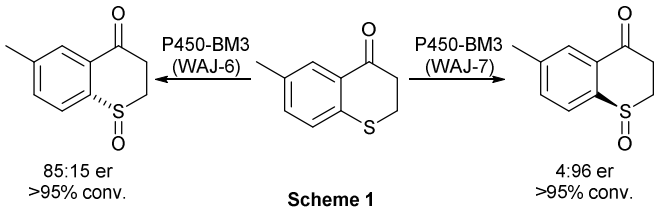
An entire issue of *Advanced Synthesis and Catalysis* (2017, **359**, Issue 12) has been dedicated to the recent developments in biocatalysis and include studies by Reetz and co-workers who showed that saturation mutagenesis of the monooxygenase P450-BM3 leads to enhanced or a reversal of the enantioselectivity of sulfoxidation of 1-thiochroman-4-ones (Scheme 1).[27] The first total synthesis of the norditerpenoid alkaloid nigelladine A **38** has been achieved using an engineered cytochrome P450 to perform a late-stage C-H oxidation (Scheme 2).[28] While traditional synthetic methods proved non-selective, the engineered cytochrome P450 enzyme allowed chemo- and regioselective allylic C-H oxidation.

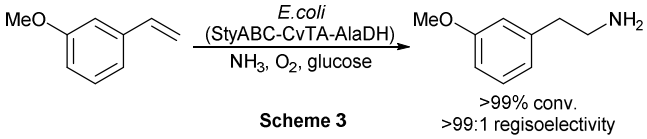


Scheme 1

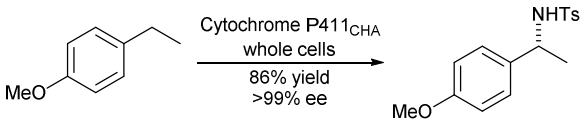
Scheme 2 **38**

Two biocatalytic methods involving one-pot enzyme cascades have been developed for anti-Markovnikov hydroamination and hydration of aryl alkenes.[29] The co-expression of an *E.coli* strain with styrene monooxygenase (SMO), styrene oxide isomerase (SOI), ω-transaminase and alanine dehydrogenase allowed the hydroamination of aryl akenes in high conversion and excellent anti-Markovnikov selectivity (e.g. Scheme 3), while a similar co-expression of SMO, SOI with a phenylacetaldehyde reductase led to the preparation of terminal alcohols. Directed evolution of an iron-containing cytochrome enzyme has resulted in a biocatalyst capable of highly enantioselective intermolecular amination of benzylic C-H bonds

(Scheme 4).[30] As iron complexes are generally poor catalysts for C-H amination, it is believed that the enzyme's protein framework provides function that the iron cofactor cannot achieve alone.

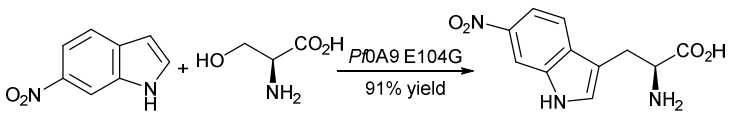


Scheme 3

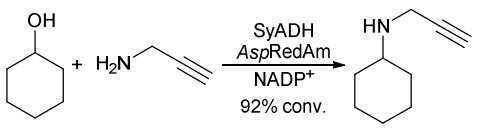


Scheme 4

Directed evolution has also been performed on the enzyme TrpB for the preparation of tryptophan analogues via the PLP-dependent reaction of serine with indoles.[31] Mutation of a universally conserved and mechanistically important residue, E104 led to biocatalysts that could catalyse coupling reactions with even weak indole nucleophiles bearing electron-withdrawing nitro (Scheme 5) and cyano groups. One-pot direct alkylation of amines has been achieved using a biocatalytic hydrogen borrowing strategy.[32] This redox neutral cascade involves the oxidation of the alcohol with an alcohol dehydrogenase (e.g. SyADH, Scheme 6), followed by transformation to the amine using reductive aminase from *Aspergillus oryzae*. With only water as a by-product, the process allowed access to a wide range of products, including chiral amines directly from racemic alcohol precursors.



Scheme 5



Scheme 6

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